Communications to the Editor

Total Synthesis of the C-Nucleoside *dl*-Showdomycin by a Diels-Alder, Retrograde Dieckmann Strategy

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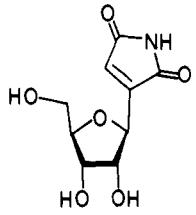
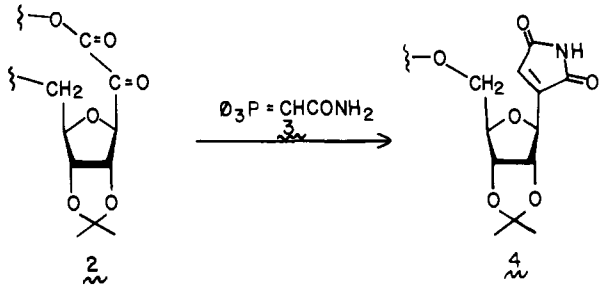
Showdomycin is a structurally unique natural product first isolated from *Streptomyces showdoensis* by Nishimura and coworkers.[1] This member of the C-nucleoside family has held a



Showdomycin (1)

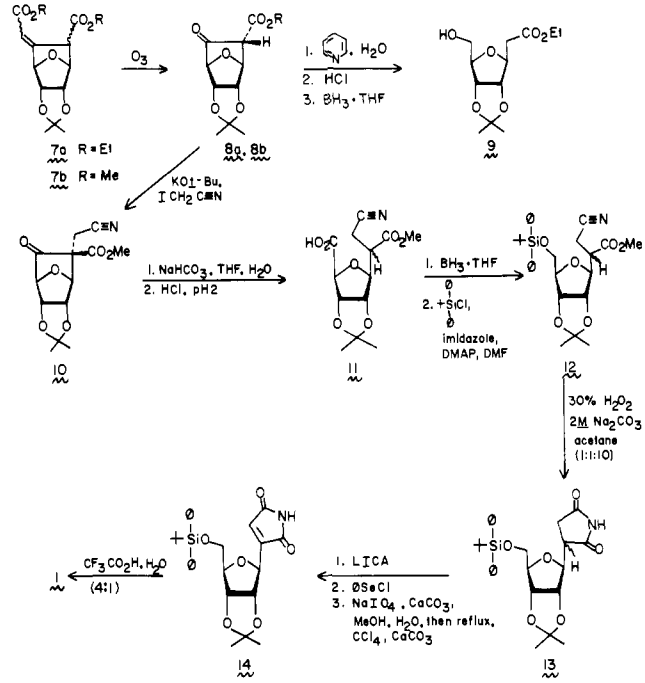
long-standing interest among investigators because of its antibiotic and antitumor activity.[2] Two *total* syntheses of showdomycin have already been accomplished by the research groups of Just and Noyori. The former workers assembled the ribose "subunit" of this molecule from furan by a Diels-Alder reaction with methyl β-nitroacrylate,[3] whereas the latter workers employed the cycloadduct derived by [3 + 4] cycloaddition reaction between an oxyallyl species and furan.[4] Both of these groups constructed the other heterocyclic subunit of this product, the maleimide, by Wittig reaction between an α-keto ester or α-keto lactone and (carbamoylmethylene)triphenylphosphorane. The use of this



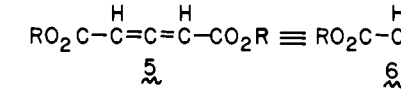
reagent for maleimide construction in the C-nucleoside series was first reported by Moffatt and Trummlitz in their semisynthetic approach to showdomycin.[5]

We now describe a total synthesis of showdomycin in racemic form, which defines a simple, new route to the maleimide subunit of this antibiotic.

Scheme I. Synthesis of *dl*-Showdomycin



We had reported that 1,3-dicarboalkoxyallene can function as a carboalkoxyketene equivalent in the Diels-Alder reaction.[6]



Carboalkoxyketene Equivalent

Thus, using furan as the diene component, the cycloadduct generated in 97% yield on reaction with **5** (50 °C, PhH, 62 h or with $AlCl_3$ catalysis, PhH, room temperature, 1 h in 90% yield) was hydroxylated (OsO_4, 30% H_2O_2, *t*-BuOH, 22 h, quantitative yield), the diol protected as its acetonide ($CuSO_4$, *dl*-10-camphorsulfonic acid, 2,2-dimethoxypropane, acetone, 68% yield), and the exo-ene unit of **7** cleaved by ozonolysis (O_3, CH_2Cl_2, −78 °C with dimethyl sulfide workup, 70% yield) to give **8** (Scheme I). The β-keto ester so derived was found to undergo a facile C–C bond scission reaction (retrograde Dieckmann reaction) upon exposure to a mixture of pyridine and water. The acid ester produced was reduced selectively by borane in tetrahydrofuran to yield compound **9**, a protected form of ethyl β-ribofuranosylacetate.[7]

From this stage, it is relatively easy to see that assembly of showdomycin requires that β-keto ester **8** be alkylated with a two-carbon unit of appropriate oxidation state and, if possible, containing a nitrogen atom. Both α-bromoacetamide and iodoacetonitrile[8] were thus examined as potential alkylating agents. With the former compound, the alkylation reaction took a strange and as yet unelucidated course.[9] With the nitrile, however,

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(2) Suhadolnik, R. J. "Nucleoside Antibiotics"; Wiley-Interscience: New York, **1970**; p 354. Danes, G. D., Jr.; Cheng, C. C. *Proc. Med. Chem.* **1976**, *13*, 303.

(3) Just, G.; Liak, T. J.; Lim, M.-I.; Potvin, P.; Tsantrizos, Y. S. *Can. J. Chem.* **1980**, *58*, 2024.

(4) Noyori, R.; Sato, T.; Hayakawa, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2561.

(5) Trummlitz, G.; Moffatt, J. G. *J. Org. Chem.* **1973**, *38*, 1841.

(6) Kozikowski, A. P.; Floyd, W. C.; Kuniak, M. P. *J. Chem. Soc., Chem. Commun.* **1977**, 583.

(7) Kozikowski, A. P.; Floyd, W. C. *Tetrahedron Lett.* **1978**, 19.

(8) The iodoacetonitrile was prepared from commercially available chloroacetonitrile by the standard Finkelstein method and was purified by bulb-to-bulb distillation (oven temperature 78 °C, 13 torr). This reagent can also be purchased from the Aldrich Chemical Company.

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C-alkylation could be accomplished in excellent yield (95%) at room temperature by using potassium *tert*-butoxide as base in tetrahydrofuran (**10**, mp 167.5–168.0 °C; *m/e* 281.0899). This experiment underscores the real virtue of **8**. *Its anion is, in fact, stable enough such that under the alkylation conditions no β-elimination of the bridging heteroatom occurs.*[10] Attempts to perform similar sorts of alkylation reactions with the ribofuranosylacetate derivative **9** are troublesome, for it has been well established that β-elimination does occur in this case with scrambling of stereochemistry at the "anomeric" center.[11]

The alkylated β-keto ester intermediate **10** dissolved in a 1:1 mixture of tetrahydrofuran and water was now fragmented by the action of a saturated aqueous sodium bicarbonate solution (30 min, room temperature). Acidic workup gave in quantitative yield the acid ester **11**[12] which was reduced in turn with borane–tetrahydrofuran to furnish the corresponding alcohol (72% yield). Protection of the hydroxyl group by silylation (*t*-$BuPh_2SiCl$, imidazole, 4-(dimethylamino)pyridine, DMF, 92% yield) to give **12** set the stage for construction of a succinimide. This ring forming reaction was accomplished in a single step by treatment of **12** at room temperature with a 1:1:10 mixture of 2 M Na_2CO_3, 30% H_2O_2, and acetone.[13] On reduction of the excess peroxide with sodium bisulfite the dihydro analogue of showdomycin **13** was obtained as a mixture of diastereomers in 73% yield [*m/e* 452.1529 ($M^+ - t$-Bu)]. The 300-MHz ^1H NMR of **13** compared favorably with the spectrum of an authentic sample of the protected form of dihydroshowdomycin synthesized from the natural product by hydrogenation over palladium.[14]

For completion of the scheme, a minor adjustment of the oxidation state of the nitrogen heterocycle and, lastly, deprotection of the hydroxyl groups were required. While a number of obvious and not so obvious reagents were considered which might effect the dehydrogenation reaction in a single step, such methods had either been examined by others before[15] or else failed when attempted in our hands. We thus resorted to a conventional selenenylation–selenoxide elimination sequence.[16] Treatment of **13** with 3 equiv of lithium isopropylcyclohexylamide at −78 °C for 20 min followed by the addition of 3.2 equiv of phenylselenenyl chloride at the same temperature with slow warming to −20 °C gave a crude mixture of selenenylated products. The mixture was oxidized directly with sodium periodate in methanol–water (5:2) and then refluxed in carbon tetrachloride in the presence of calcium carbonate to effect selenoxide elimination. The protected form of showdomycin was generated in 90% yield on the basis of consumed starting material [*m/e* 450.1373 ($M^+ - t$-Bu)]. Deprotection of the hydroxyl groups by treatment with a 4:1 trifluoroacetic acid–water solution at room temperature for 1.5 h completed the synthesis of **1**.[17]

Further work is now in progress to generate **1** in optically active form from an optically active allene and extend our scheme to the preparation of some new *C*-nucleoside isosteres.

Acknowledgment. This work was supported by the National Institutes of Health through Grant CA22612-03. The 300-MHz Bruker NMR instrument used in these studies was purchased through funds provided by the National Science Foundation (Grant CHE-79-05-185). We thank Dr. Mitsuru Yoshioka of Shionogi Laboratories for the authentic sample of showdomycin.

Supplementary Material Available: TLC, mp, IR, 300-MHz ^1H NMR, and MS data of all new compounds (5 pages). Ordering information is given on any current masthead page.

(9) An X-ray analysis of this material is now being carried out, and the results of this study will be reported in due course.
(10) The β-elimination reaction has been examined with the cycloadducts formed from **5** and furans or pyrroles as a route to fused heterocycles: Kozikowski, A. P.; Kuniak, M. P. *J. Org. Chem.* **1978**, *43*, 2083.
(11) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.
(12) No attempt has presently been made to resolve this acid, although it should clearly be possible in light of Noyori's work.[4]
(13) Liberek, B. *Chem. Ind. (London)* **1961**, 987.
(14) We thank Dr. Nakagawa of Shionogi Laboratories for an NMR spectrum of the acetonide of dihydroshowdomycin.
(15) Rosenthal, A.; Chow, J. *J. Carbohydr. Nucleosides, Nucleotides* **1980**, *7*, 77.
(16) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.
(17) The synthetic material was identical in all respects (^1H NMR, IR, MS, and TLC data) with a sample of the natural product obtained from Shionogi Laboratories.

Oxo–Peroxo Oxygen Exchange in Peroxovanadium(V) and Peroxomolybdenum(VI) Compounds

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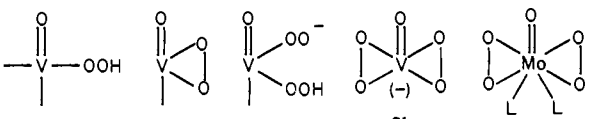
Recent studies on the vanadium(V)-catalyzed oxidation of sulfides by hydrogen peroxide in ethanol and dioxane–ethanol have shown that monoperoxo- (**1**) and diperoxovanadium(V) species (**2**), the latter as an anion, are formed under appropriate circumstances.[1-3] In particular, monoperoxo appears to be the only species present in dioxane–2.5% ethanol (v/v), even at high $[H_2O_2]/[V^V]$ ratio, whereas in ethanol solvent the monoperoxo is prevalent only at low hydrogen peroxide concentration.

The structure of peroxo species in solution is still uncertain:[4] they may have either the open structure **1a**, **2a** or the cyclic ones **1b**, **2b**; equilibrium interconversion between open and cyclic



1a **1b** **2a** **2b** **3**

structures may also occur. Thus, the identification of the real oxidizing species in these metal-catalyzed processes is of current interest.

We have found that, under conditions where **1** is the only peroxo species present[3] or at least the dominant one, ^{18}O labeled hydrogen peroxide undergoes a fairly fast oxygen exchange (~50% label loss in 10–20 h at 25 °C).

Molybdenum(VI) peroxo species exhibit similar reactivity in sulfide and olefin oxidation.[5] They are thought to have a similar structure, i.e., **3**. Thus, we tested their ability to catalyze the oxygen exchange reaction, and indeed, we observed with Mo(VI) catalyst, too, the same reaction, though it occurs at a quite slower rate (~50% label loss in 100 h at 40 °C). A selection of the results so far obtained is reported in Table I.

In the general procedure, 6×10^{-3} M solution of H_2O_2 of appropriate enrichment[6] (see Table I) in the indicated solvent containing the catalyst[7] (1×10^{-4} M) and variable amounts of water (either added or contained in the solvents and reagents used or both) were allowed to react in a thermostatic bath under

(1) Di Furia, F.; Modena, G. *Recl. Trav. Chim. Pay-Bas*, **1979**, *98*, 181.
(2) Bortolini, O.; Di Furia, F.; Scrimin, P.; Modena, G. *J. Mol. Catal.* **1980**, *7*, 59.
(3) Bortolini, O.; Di Furia, F.; Modena, G.; Scrimin, P. *J. Mol. Catal.* **1980**, *9*, 323.
(4) Side-bonded peroxo compounds of vanadium(V) (Wieghardt, K. *Inorg. Chem.* **1978**, *17*, 57) have been reported, which have, however, ligand environment and formal charge different from **1b**.
(5) Bortolini, O.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1981**, *11*, 107.
(6) The ^{18}O-enriched hydrogen peroxide was prepared by direct conversion of $H_2{}^{18}O$ vapor in an electric discharge. For details, see: Ball, R. E.; Edwards, J. O.; Jones, P. *J. Inorg. Nucl. Chem.* **1966**, *28*, 2458.
(7) $VO(acac)_2$ and $MoO_2(acac)_2$ were used. Vanadyl acetylacetonate in ethanol undergoes fast and irreversible oxidation,[1] yielding triethyl vanadate, $VO(OEt)_3$. The displacement of one or both the acetylacetone ligands from $MoO_2(acac)_2$ in EtOH has been previously observed. See: Di Furia, F.; Modena, G.; Curci, R.; Edwards, J. O. *J. Chem. Soc.*, **1980**, *Trans. 2*, 457.

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